used for immunotherapy or can be used in methods of diagnosis.

REMARKS

Claims 1, 46-47, 54-58, and 69-72 are pending.

The Office Action has stated that the pending claims appear to be free of the art.

The specification has been amended at pages 1 and 57 to change the title of the Application, as requested in the Office Action.

As requested in the Office Action, the specification has also been amended at page 1 to correct the priority information.

The specification has also been amended at pages 3-5 to recite the different parts of the drawings, as requested in the Office Action.

As requested in the Office Action, the specification has been amended at pages 34-35 to provide the ATCC Accession No. HB11642 for monoclonal antibody ER4.7G11. Support for this amendment can be found in a priority document of the Application, U.S. Patent No. 5,858,358, at col. 29, lines 21-25, which has been incorporated by reference into the Application.

As requested in the Office Action, the specification has also been amended at page 57 to more adequately describe the claimed invention.

Pursuant to the provisions of 37 C.F.R. §1.121(b)(1)(iii), a marked-up copy of amended specification is attached herewith as Appendix A.

None of the above amendments adds any new matter to the Application as filed.

Each of the issues raised in the Office Action are addressed below.

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I. Sequence Statement

The Office Action has asserted that the Application does not comply with the requirements of 37 C.F.R. §1.821-1.825.

To overcome this objection, Applicants make the following statement.

Pursuant to 37 C.F.R. §1.821(f), I, as Applicants' representative, hereby state that the contents of previously submitted "Sequence Listing" in computer-readable form are identical to those of the "Sequence Listing" in paper form submitted herewith. As required by 37 C.F.R. §1.821(g), I also state that the submission adds no new matter to the Application as filed.

II. Amendments to the Specification

The Office Action has requested amendment of the specification.

To comply with the Office Action, the Applicants have made the following amendments to the specification.

The specification has also been amended such that the different numbers of the drawings are recited.

The title of the Application has been amended to more clearly describe the claimed invention. Enclosed herewith is a Petition to Correct the Filing Receipt of the Application which includes the present amendment to the title.

The abstract of the Application has been amended to more clearly describe the claimed invention.

The specification has been amended to remove Applicants' claim to priority to U.S. Serial No. 07/275,433, filed November 23, 1988.

The specification has been amended at page 35 to provide the ATCC Accession No. HB11642 for monoclonal antibody ER4.7G11.

III. Priority Document

Applicants have amended the specification to remove the priority claim of the Application to U.S. Serial No. 07/275,433, filed November 23, 1988. Enclosed herewith is a Petition to Correct the Filing Receipt of the Application which includes the present amendment to the priority claim.

IV. 35 U.S.C. §112, First Paragraph, Rejections

Claims 1, 46-47, and 56-58 stand rejected under 35 U.S.C. §112, first paragraph, because "there is insufficient written description encompassing 'a ligand which binds to the accessory molecule CD9' because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of [both] the 'ligand' are not set forth in the specification as filed, commensurate in scope with the claims." (Office Action, paragraph 10, page 4).

Applicants respectfully traverse this ground for rejection.

Applicants' invention stems from their discovery that if the CD9 accessory molecule is stimulated on a CD8+ cell activated via its T cell recptor/CD3 complex, then that CD8+ T cell will be induced to proliferate. As Applicants knew, and those of ordinary skill at the time of filing would have known upon reading the specification, the anti-CD9 antibody described in the specification is merely used to mimic the role that the naturally occurring CD9 ligand plays in vivo. Applicants respectfully point out that induction of CD8+ cells proliferation normally occurs in vivo; however, ordinary skilled biologists know that most healthy individuals do not have autoantibodies directed against self CD9. Thus, normal CD8+ T cell proliferation occurs in vivo when the CD9 molecule on the CD8+ T cell is stimulated by its naturally occurring ligand.

Thus, Applicants respectfully aver that the invention, as claimed, was conceived at the time of the filing of the Application.

Moreover, Applicants respectfully aver that those of ordinary skill at the time the Application was filed would have known the critical common structural attributes of a ligand for CD9 other than CD9-specific antibodies. These attributes, namely, are the ability of the ligand to bind to and stimulate a CD9 molecule on the surface of a CD8+ T cell. To serve this purpose (namely to bind and stimulate CD9 on the surface of a CD8+ T cell, those of ordinary skill would understand that any ligand, including any CD9-specific antibody, may be employed.

Applicants further note that it is through its ability to bind to CD9 that the anti-CD9 antibody described in the specification is able to mimic the naturally occurring in vivo ligand of CD9. Thus, other attributes of a CD9-specific antibody, or antibodies in general, such as ability to fix complement and the ability to be bound by an Fc receptor, are irrelevant with regard to the present invention, as the ordinary skilled artisan would have realized at the time the Application was filed. Rather, it is merely the attribute of binding to CD9 that characterizes a CD9-binding ligand of the invention, as the ordinary skilled artisan would have understood at the time the Application was filed. Thus, the ordinary skilled artisan would have understood that an anti-CD9 antibody is merely a non-example of such a CD9 ligand. As the Federal Circuit stated recently, "if a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of the filing, even if [not] every nuance of the claim is explicitly described in the specification, then the adequate written description requirement is met." In re Alton, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

Finally, Applicants note that they are not disputing that an amino acid change to an antibody may alter that antibody's binding specificity. In fact, it is upon this very specificity that Applicants' are relying—Applicants' claimed invention covers a CD9-

binding ligand, such as a CD9-specific antibody, so long as that ligand actually binds to CD9.

Based on these remarks, Applicants respectfully request reconsideration and withdrawal of this ground for rejection.

Claims 1, 46-47, and 56-58 also stand rejected under 35 U.S.C. §112, first paragraph, because the specification "does not reasonably provide enablement for any 'CD9-specific ligand' to be employed in the claimed method." (Office Action, paragraph 11, page 6).

Applicants respectfully traverse this ground for rejection.

As discussed above, those of ordinary skill in the art at the time the Application was filed would have known that the CD9-binding antibody described in the specification is a non-limiting example of a CD9-binding ligand. Ordinary skilled artisans, at the time the Application was filed, would have known that any structural characteristics of a CD9-binding ligand, aside from those features necessary to allow binding to CD9, are irrelevant to the Applicants' invention. Rather, those of ordinary skill in the art at the time the Application was filed would have known that the only structural characteristic necessary for a CD9-binding ligand is that the ligand actually bind to and stimulate CD9, as is recited by the claims.

Applicants note also that ordinary skilled artisans, at the time the Application was filed, would have known that any CD9-binding ligand, regardless of its structural characteristics, falls within the claimed invention so long as it actually binds to and stimulates CD9. Thus, ordinary skilled artisans would have recognized that an antibody that does not bind to CD9, even though it shares many structural characteristics with a CD9-binding antibody (e.g., both are immunoglobulin proteins), is not within the claimed invention.

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Based on these remarks, Applicants respectfully request reconsideration and withdrawal of this ground for rejection.

V. 35 U.S.C. §112, Second Paragraph, Rejections

Claims 1, 46-47, and 54-58 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite as failing to recite essential steps.

Applicants respectfully traverse this ground for rejection.

Applicants respectfully point out that the T cells are stimulated upon contact by an anti-CD3 antibody. Thus, the mere addition of an anti-CD3 antibody (or any ligand that binds to the TCR/CD3 complex) to a population of T cells will necessarily stimulate the T cells.

In addition, the CD9 accessory molecule on the T cells is stimulated upon binding by that molecule by a CD9-binding ligand (such as a CD9-binding antibody).

Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground for rejection.

VI. Double Patenting

Claims 1, 46-47, 54-58, and 69-72 stand rejected under the judicially created doctrine of obviousness-type double patenting with regard to claims 1-33 of June et al., U.S. Patent No. 5,858,358.

Applicants respectfully request this ground for rejection to be held in abeyance in the Application until the claims are deemed allowable. If, at that time a double patenting rejection exists, Applicants will file a terminal disclaimer over June, et al., U.S. Patent No. 5,858,358.

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CONCLUSION

Applicants respectfully submit that the claims appear to be in condition for allowance. However, if the Examiner believes that any further discussion of this communication would be helpful, the Examiner is encouraged to contact the undersigned by telephone.

In accordance with the provisions of 37 C.F.R. §1.136(a)(1), Applicants enclose herewith a petition requesting a three-month extension of time, up to and including April 1, 2002, to respond to the outstanding Office Action. Please apply the three-month extension of time fee of $920.00 to our Deposit Account No. 08-0219.

No additional fees are believed to be due in connection with this communication. However, please apply any additional charges, or credit any overpayment, to our Deposit Account No. 08-0219.

Respectfully submitted,
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APPENDIX A

Marked-Up Copy of Amended Specification Pursuant to 37 C.F.R. § 1.121(b)(1)(iii)

At page 1, lines 3-4:

METHODS FOR SELECTIVELY STIMULATING PROLIFERATION OF CD8+ T CELLS

At page 1, lines 7-17:

This application is a continuation application of U.S. Patent No. 5,858,358, issued on January 12, 1999, which in turn is a continuation-in-part of the following U.S. applications: U.S. Serial No. 08/073,223, filed June 4, 1993, entitled "Methods for Selectively Stimulating Proliferation of T cells"; U.S. Serial No. 07/864,805, filed April 7, 1992, entitled "CD28 Pathway Immunoregulation"; U.S. Serial No. 07/864,866, filed April 7, 1992, entitled "Enhancement of CD28-Related Immune Response"; and U.S. Serial No. 864,807, filed April 7, 1992, entitled "Immunotherapy Involving Stimulation of Th CD28 Lymphokine Production". [Each of these applications is a continuation-in-part of U.S. Serial No. 275,433, filed November 23, 1988, entitled "Immunotherapy Involving CD28 Stimulation", which corresponds to International Application Serial No. PCT/US89/05304 (Publication No. WO 90/05541) filed November 22, 1989.] The contents of each of these applications is incorporated herein by reference.

At page 3, lines 31-35:

Figure 5 depicts fluorescent activated cell sorter analysis (FACS) in which cells were stained after isolation (day 0, [panel] Fig. 5A), or after 26 days in culture with either CD28 stimulation ([panel] Fig. 5B) or IL-2 culture ([panel] Fig. 5C), with phycoerythrin conjugated antin-CD3, CD4, CD8 or with an IgG2a control monoclonal antibody and fluorescence quantified with a flow cytometer.

At page 3, lines 36 through page 4, line 2:

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Figure 6 shows FACS analysis of the EX5.3D10 monoclonal antibody depicting reactivity with CD28 in comparison to an anti-CD28 monoclonal antibody 9.3. The flowing cell lines were tested: [Panel] Fig. 6A, untransfected CHO-DG44 cells; [Panel] Fig. 6B, CHO-HH cells; [Panel] Fig. 6C, unactivated peripheral blood lymphocytes; and [Panel] Fig. 6D, Jurkat No. 7 cells.

At page 4, line 3-6:

Figure 7 shows FACS analysis of the ES5.2D8 monoclonal antibody depicting the binding reactivity with the following cell lines: [Panel] Fig. 7A, CHO-DG44 cells; [Panel] Fig. 7B, CHO-105A cells; [Panel] Fig. 7C, unactivated human peripheral blood lymphocytes; and [Panel] Fig. 7D, PMA activated peripheral blood lymphocytes.

At page 5, line 1-3:

Figure 18 show FACS analysis of the monoclonal antibody ES5.2D8 ([panels] Figs. 18C and D) or a control IgG ([panels] Figs. 18A and B) depicting the binding reactivity with MOP cells transfected with a plasmid encoding the CD9 antigen.

At page 35, line 36 through page 36, line 9:

Experiments were conducted to determine whether a population of $CD8^+$ T cells could be preferentially expanded by stimulation with an anti-CD3 mAB and a monoclonal antibody 2D8. $CD28^+$ T cells were obtained essentially as described in Example 1. To assay for CD8 expression, a primary anti-CD8 antibody and a labeled appropriate secondary antibody were used in FACS analysis to determine the percent positive cells. As shown in FIG. 17, at day 7 following stimulation of T cells with the anti-CD3 mAb G19-4sp and the mAb 2d8, the $CD8^+$ fraction had increased from approximately 20% to over 40%. Another monoclonal antibody ER4.7G11 (referred to as 7G11) was also found to stimulate $CD8^+$ T cells. This antibody was raised against recombinant human CTLA4 and has been deposited with the ATCC on Jun. 3, 1994 at Accession No. [_____] HB11642. This result indicates that binding of either a distinct

region of CTLA4 or of a cross-reactive cell surface protein selectively activates $CD8^+$ T cells.

At page 57, lines 1-2:

METHODS FOR SELECTIVELY STIMULATING PROLIFERATION OF CD8+ T CELLS

At page 57, lines 6-14:

Methods for inducing a population of $CD8^+$ T cells to proliferate by activating the population of $CD8^+$ T cells and stimulating a[n] CD9 accessory molecule on the surface of the T cells with a ligand which binds the accessory molecule are described. T cell proliferation occurs in the absence of exogenous growth factors or accessory cells. T cell activation is accomplished by stimulating the T cell receptor (TCR)/CD3 complex or the CD2 surface protein. To induce proliferation of an activated population of T cells, an accessory molecule on the surface of the T cells, such as CD28 or CD9, is stimulated with a ligand which binds the accessory molecule. The T cell population expanded by the method of the invention can be genetically transduced and used for immunotherapy or can be used in methods of diagnosis.